Psychopharmacology and Conditional Reflexes

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Abstract—Drugs may be used in several ways to investigate their role in behavior. (1) The placebo effect is usually connected with the relation of the person to the drug. (2) Using the drug as an unconditional stimulus, its action may help to analyze the role of peripheral vs. central stimuli in the formation of conditional reflexes; our work has shown that the effect of drugs which act solely at the peripheral nerve endings without the involvement of the central nervous system cannot become conditioned. (3) The action of drugs on the conditional reflex (CR) compared with their action on the unconditional reflex (UR) explains some of their behavioral effects. (4) Schizokinesis is often prominent in the action of drugs. Although a drug may increase the level of the heart rate, for example, it can, on the other hand, diminish the reactivity shown in the CR. Meprobamate and mescaline affect differently the cardiac and the motor components of the CR, illustrating a schizokinesis. (5) The type of individual is an important factor in the action of drugs; the same drug may have opposite effects on different individuals. This leads to the conclusion that a drug should fit the individual as well as the disease. (6) Autokinesis is often seen in drug action. Therefore a single dose of some drugs, such as acetylcholine, epinephrine or LSD, may permanently change the relationships between excitation and inhibition, in the direction of improvement or deterioration (positive or negative autokinesis).

I. Effect of Person

One of the best known actions of drugs is the placebo effect. In this way the drug is a signal, a conditional stimulus for whatever role the *person* plays in his association with another individual. To understand this placebo effect one has to understand what we call the Effect of Person.

This effect is complex. The person may have functioned in some past relationship with the patient or the patient has some faith in the person administering the drug. Aside from this well-recognized role of the person, there is another aspect of person which can be extremely important but which at present is very poorly understood. Throughout nature, the influence of one individual upon another is profound, and apparently related to some inborn function of the nervous system or it is perhaps hormonal. This relationship to another individual may be positive or negative. An example of the former, where the very existence of life depends upon some obscure effect connected with the mere presence of other individuals, especially those of the same species of a close relationship, is seen in

the manifold relations of the newborn with its mother. Such relationships create a definite emotional state which may be considered positive and conducive to life. They exist among individuals on as low a scale as the insects. Their mechanisms are poorly understood. They may depend upon unknown radiations as postulated by some Russians (Gurevich, *et al.*, 1961, Lamb and Isaacs, 1969).

Other relations between individuals may produce the opposite type of emotion—flight or fight. Most individuals arriving at a certain age tend to avoid or be afraid of other living individuals, usually those with which they are not familiar. These complex relationships of Effect of Person seem to be—in contrast with those in which the Person is a signal (acquired)—instinctual, in the nature of unconditional reflexes. Maturation and the age of the individual are major influences. Thus, fledgling birds in the nest are receptive apparently indiscriminately to a range of other individuals, parent bird or human; they stretch wide the mouth to receive food. But once the bird is out of the nest and able to fly, it immediately avoids individuals not of its own kind.

The influence of *imprinting* should be emphasized here; this principle has been copiously elaborated on by Konrad Lorenz. The late Howard Liddell showed the influence of the presence of the mother in newborn lambs; if the lamb did not begin nursing its mother within a few hours, the mother thereafter would refuse its offspring. It is a well-known observation that most cows will not accept any other calf but their own. The general principle of the influence of one individual on another is so universal it hardly requires substantiation, but as a principle it is not sufficiently recognized in behavioral studies.

In our laboratory we have shown that the presence of the person can be used in the same way as an unconditional stimulus. The heart rate reveals the Effect of Person when the general behavior shows no observable change. Thus it is very important to have a delicate measure such as the cardiovascular function, skin resistance, etc. In dogs Stephens (Gantt, *et al.*, 1966) showed that the ringing of a bell to which the dog is not accustomed produces an increase in heart rate, while in the same dog the influence of petting (rubbing the dog behind the ear) lowers the heart rate. But after two weeks using the bell as a signal for petting, the bell changes its role from a tachycardiac agent to a bradycardiac one. Newton and I (1968) have shown that in a pathological, catatonic type dog (V-3) the mere presence of a person will reduce its heart rate from about 150 beats/min down to as low as 20, and its blood pressure

will drop from 150 to 75. Newton and Ehrlich (1969) have demonstrated that the coronary blood flow in the presence of a person will be increased to a greater extent than is the coronary blood flow in the same dog when hungry and eating.

The physician knows the Effect of Person—though in modern medicine this influence is not sufficiently recognized. Osler mentioned that a cancer patient gained ten pounds as a result of the visit of an optimistic physician.

The same person may influence different dogs in different degrees or different people may influence the same dog in markedly different degrees as shown by Royer and Ellen Brown (Gantt *et. al.*, 1966). In the above cases the people whose influence was tested had had no previous relationship to these dogs.

II. Peripheral and Central Acting Drugs

Related to the placebo action of drugs is the question of which drugs can serve as the basis for forming a conditional reflex, not in connection with the association of the drug with the person, but considering its unconditional reflex action. Atropine, among its other actions, produces a marked tachycardia. According to pharmacologists, this is caused by the blocking of vagal impulses peripherally at the neuromuscular junction in the heart, and not through any central nervous system influences. There are many such drugs which we have employed for their peripheral action—pilocarpine on salivary and other secretions, acetylcholine (ACh) for its inhibitory action on heart rate (Teitelbaum, Gantt, Stone, 1965), and phloridzin to produce glycosuria through its action at the renal level (Livingston and Gantt, 1965).

On the other hand, there are drugs whose primary effect is produced through central nervous system involvement: morphine on sleep, apomorphine to produce vomiting, bulbocapnine to produce catatonia and EKG pattern changes (Perez-Cruet and Gantt, 1964). Where the action of the drug is mediated peripherally and not through CNS involvement, this action has never, in our experiments, been formed as a conditional reflex (Loucks, 1937, MacKenzie, 1950, Teitelbaum, 1956, Perez-Cruet, 1959, and Livingston, 1965). The effect of drugs whose action is produced without involvement of the central nervous system is not modifiable through repetition of the conditioning process. Drugs used in this way, as well as electrical stimuli, have been instrumental in revealing the role of the periphery and of the center in the formation of conditional reflexes.

Table 1 illustrates which drugs and agents can become the basis for a CR. It is seen that in no case can the effect of a drug which is due solely to a peripheral action become a CR, while in nearly every case those actions which are mediated through the central nervous system can become CRs.

There is a further consideration as to whether the drug is used in operant conditioning or in classical conditioning. Although Asratyan, Gantt and others consider that there is no major difference between the mechanisms of the so-called Pavlovian classical conditioning and those of operant conditioning (Asratyan, 1967), some work has been done indicating that in one case the drug effect can become a conditional reflex, but not in the other. Using carbon dioxide as an unconditional stimulus in pigeons, Weinstein (1966) found that its effect was not conditionable, while with the same drug used as the basis for operant conditioning, it was possible to form a conditional reflex. This work has not been sufficiently elaborated to justify a conclusion, and the establishment of any principle of a discrepancy in classical and operant conditioning other than can be attributed to a variation of method awaits confirmation.

III. Effect on Conditional Reflexes and Unconditional Reflexes

The action of drugs may be considered from the viewpoint of how they change an activity that is not under special stimulation, e.g., resting heart rate, and how they modify the same function when it is part of a conditional reflex. To begin with the action of one of the most familiar pharmacological beverages and agents, viz., alcohol, we are well aware that it may exaggerate the unconditional reflexes, producing in not too large doses increased motor activity, tachycardia, tachapnea and diuresis. These are all unconditional reflex actions. But when we study the effect of alcohol on the conditional reflexes the action may be entirely different. Thus alcohol usually diminishes the degree of the conditional reflex (CR) intensity and amplitude—motor, secretory and cardiac—and it converts the inhibitory CR into an excitatory one. This is an action on the acquired reactivity rather than on an unconditional reflex level.

Some of the tranquilizers which we have studied show the same thing. Chlorpromazine and reserpine may decrease the level of heart rate, while meprobamate often produces a tachycardia (Gliedman and Gantt, 1956). But the action of these tranquilizers on the conditional reflex activity is opposite to what it is on the

TABLE 1. Relation of Drug Activity to CR Formation

1 Drug or Agent	2 Function Measured	3 UR	4 Site of Action	5 CR Formation	6 Reference
Food	Saliva, motor	Salivary sec. Body movement	CNS	Yes	Pavlov
Pilocarpine	Secretory	Salivary increase	Local	No	Crisler
Pilocarpine	Secretory	Prostatic sec.	Local	No	Rienhoff and Gantt
Sexual stim., direct	Sexual	Ejaculation, sperm count, latent period and erection duration	CNS	Yes	Gantt
Neurotic state	Sexual, respiratory	Ejaculation, sperm count, latent period and erection duration	CNS	Yes	Gantt
Food	Gastric sec.	Gastric sec.	CNS	Yes	Pavlov
Histamine	Gastric sec.	Gastric sec.	Local	No	Gantt, *et al.*
Food	Alimentary	HR, BP	CNS	Yes	Gantt, *et al.*
Atropine	CV	HR, BP	Local	No	MacKenzie and Gantt
ACh	HR, BP	Decrease, then increase	Local	No	Teitelbaum and Gantt
Epinephrine	Glycemia	Increase	Local	No	Gantt, *et al.*
Fear	Gen. muscular	Twitching	CNS	Yes	Cannon
Morphine	Behavior	Sleep	CNS	Yes	Krylov and Pavlov
Apomorphine	Gastric	Vomiting	CNS	Yes	Voegtlin
Elec. stim. of intact cerv. vagus	CV, respiratory	Cough, bradycardia	Medulla (?)	No*	Andrus, *et al.*
Phloridzin	Renal	Glycosuria	Local	No	Livingston and Gantt
Water	Renal	Diuresis	CNS	No*	Watt, Livingston and Gantt
Effect of person	CV	Increase or decrease	CNS	Yes	Gantt, *et al.*
Pain	CV, somatic	Body movement, inc. BP, tachycardia	CNS	Yes	Gantt, *et al.*
Electrical stim. of:					
Cortex	Somatic musc.	Movement	CNS	Yes	Doty
Post. spinal columns	Somatic musc.	Movement	CNS	Yes	Loucks and Gantt
Cerebellum	Somatic musc.	Movement	CNS	Yes	Brogden and Gantt
Caudal end of vagus	CV	Bradycardia, dec. BP	Local	No	Pavlov Andrus, *et al.*

* Only exceptions of inability to condition stimulations involving CNS.

unconditional reflex resting level. Thus they both decrease the cardiac conditional reflex, although their action on the resting level is opposite.

Another action which is of importance is observed with these tranquilizers: meprobamate in therapeutic doses diminishes the cardiac conditional reflex, but has little effect on the motor conditional reflex, while chlorpromazine and reserpine act to about the same degree on both the cardiac conditional reflex and the motor conditional reflex (Gantt, 1968). Mescaline, opposite to the action of meprobamate, reduces the cardiac conditional reflex to a greater extent than it reduces the motor conditional reflex (Bridger, 1956).

From these considerations with drugs it appears that the drug may have a special effect on acquired habits and on conditional reflexes, which is not revealed by its effect on the function when we consider only the unconditional reflex activity. This means that in order to assess the action of a drug on behavior, we must not only take into account the usual pharmacological action but also the action on the conditional reflex. In this latter action we must examine the effect on the various components of the conditional reflex—somatic, motor, cardiovascular, secretory, etc.

The phenomenon of schizokinesis is apparent when we compare the effect of the drug on the various physiological components of a conditional reflex. Thus it may affect the motor CR but not the cardiac CR (Gantt, 1957).

IV. Pharmacology and Types

Many decades ago, Pavlov formulated the idea that on the basis of the conditional reflex activity all dogs did not react identically. He divided them into four types according to the strength and stability of the excitatory and inhibitory conditional reflexes, chiefly the secretory ones. Later Pavlov studied in great detail the action of bromides in the different types of dogs, especially on their neuroses. He found that bromides not only had a special effect on excitatory and inhibitory conditional reflexes, but that this varied with the type of dog and furthermore that there was a special relation of the amount of drug to the type of dog; in some dogs much smaller doses were effective than in others, depending upon the balance between the excitatory and the inhibitory CRs (Pavlov, 1928).

We also have seen effects in dogs according to type, especially with pathological conditions. The action of alcohol, for example, on two markedly pathological and opposite dogs, "Nick"

and "V-3," are very different. Using induced sexual reflexes in these two dogs alcohol was seen to have the conventional Shakespearian effect of inhibition in one, an excitatory, anxious type (Nick), while in the catatonic dog (V-3), alcohol had the opposite effect. In V-3, a dog in which it was impossible to induce sexual reflexes, we were able to induce sexual reflexes only under alcohol. In this dog sexual erections were produced for as long as 40 minutes under the influence of alcohol (Gantt, 1952).

Murphree and collaborators (1967) have demonstrated a very marked difference in degrees of normal and pathological pointers. Their normal dogs showed the usual bradycardia to the Effect of Person (petting). But their pathological dogs showed no modification of heart rate to the same stimulus. Here the heart rate was a function which revealed this difference in a much more prominent way than was revealed by the general behavior. In most neurotic dogs that we have studied the Effect of Person produces a greater bradycardia than in a normal type; in the pathological types which Murphree *et al.* studied there was a very diminished effect of the person on heart rate (Murphree, Peters and Dykman, 1967). It appeared that there was a kind of catatonia seen in the heart to the Effect of Person.

In these studies we see an illustration of the adage that "What is one man's meat may be another man's poison" (St. Paul). Our experiments lead us to the conclusion that in human therapy the drug should be adapted to the individual, as well as to the disease. It is quite likely that the disease pattern itself is more a result of the personality, the individual type, than it is of any specific cause. Under stress, a given individual may always show the same symptoms, while an individual of another "type" may show opposite symptoms. The pattern of symptoms reveals the personality but is less related to a specific cause. In the therapeutic application of drugs we should consider both the individual type and the dose that is applicable to that individual. This requires a special study of the action of drugs on individuals.

V. Autokinesis and Drugs

Autokinesis is a word that I have used to describe changes of reactivity that *develop* in an individual independently of what goes on in their external environment. Experimentally we have seen that when some external stimulus produces a changed reactivity in the dog, that if such a dog is allowed to rest outside the experimental environment and brought back later, that the same stimulus pro-

duces markedly different effects than these stimuli did before the rest. These effects may be in the direction of improvement or they may be in the direction of increased pathology. Also, the relations between the different physiological systems seem to have changed.

From these experiments we postulate that the external stimulations not only produce a temporary effect but that their action is stored in the brain as a potential focus of activity. These foci of excitation may very likely continue to interact among themselves unconsciously and independently of the external environment.

There is no reason to think that the whole reactivity of the organism has to do with the external environment. Why may there not be continued reactivity among these centers of excitation over a period of time? In our own experiments we have seen sometimes that one dose of a chemical agent, drug, or hormone, may produce a lasting effect on the balance between the excitatory and the inhibitory conditional reflexes. This has appeared especially in the study of acetylcholine and epinephrine. In some dogs one dose of these hormones improved the performance, the relationship between the excitatory and the inhibitory reflexes, and this improvement is maintained although the drug is not subsequently used.

It has been said sometimes that several weeks after intoxication with LSD or marijuana, in an interval free of symptoms, the patient will suddenly have a recurrence of the same symptoms he had under the drug—a "flashback." Evidently a focus of former activity which has been lying dormant has been reactivated. Here is another instance of the same phenomenon that occurs in many forms referable to the interaction among centers in the brain, namely, autokinesis.

The experimental demonstration of autokinesis has been widely demonstrated but the principle has not been universally recognized. Experiments have shown that a certain time period is required for excitations to be permanently stored in the brain. In patients with head injuries, memory of events which occurred shortly before the injury is wiped out because theoretically there has not been time for permanent storage. The experiments of Bures in Prague have shown in detail the transfer of stimulations in the brain from one hemisphere to another and the effect of cutting the corpus collosum. Tislow in Philadelphia (1967) and Tonkikh in Russia (Gantt, 1966) have reported experiments demonstrating autokinesis—the changed activity after one application of a drug. Clemente has furnished physiological data on the interaction of centers using electrophysiological methods (1968).

The phenomenon of autokinesis indicates there are developments occurring within the organism, perhaps entirely subconsciously, that continually interact and change the reactivity. This changed reactivity may influence the whole general behavior. The conditional reflex measurements made after certain elapsed periods, sometimes as long as years after the original stimulation from the external environment, gave us a qualitative measurement of these changes that have been proceeding within the organism more or less independently of the external environment.

Thus we see the important but little explored principle of autokinesis, both normally and with drugs.

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